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Published

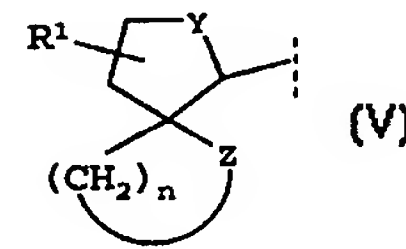
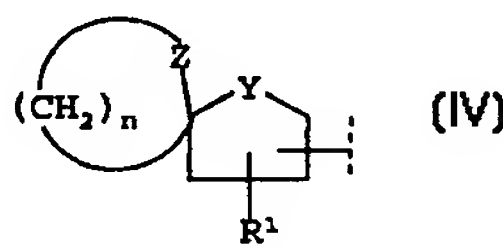
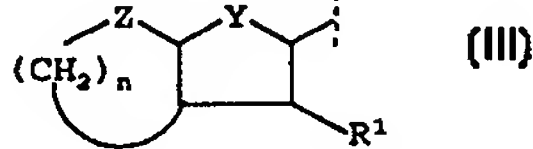
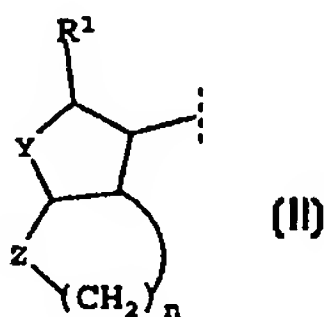
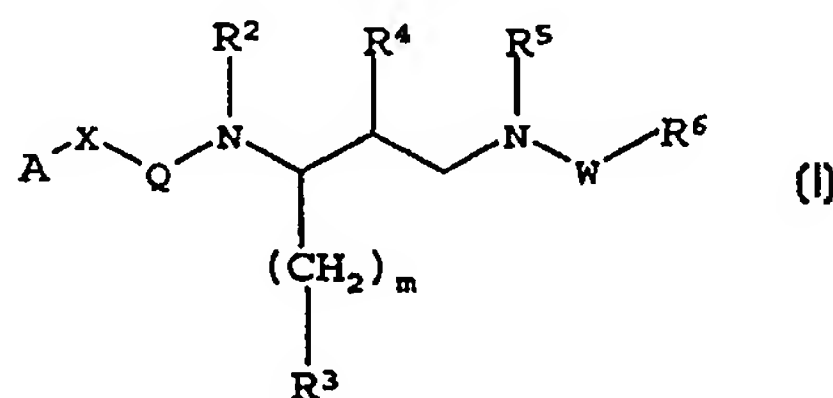
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:

10 February 2000 (10.02.00)

(54) Title: MULTI-DRUG RESISTANT RETROVIRAL PROTEASE INHIBITORS AND USE THEREOF



(57) Abstract

The present invention generally provides a retroviral protease-inhibiting compound represented by formula (I), or a pharmaceutically acceptable salt, a prodrug, or an ester thereof, wherein A is a group of formula (II), (III), (IV), or (V); R¹, R², R³, R⁵, or R⁶ is H, or an optionally substituted and/or heteroatom-bearing alkyl, alkenyl, alkynyl, or cyclic group; Y and/or Z are CH₂, O, S, SO, SO₂, amino, amides, carbamates, ureas or thiocarbonyl derivatives thereof, optionally substituted with an alkyl, alkenyl, or alkynyl group; n is from 1 to 5; X is a bond, an optionally substituted methylene or ethylene, an amino, O or S; Q is C(O), C(S), or SO₂; m is from 0 to 6; R⁴ is OH, =O (keto), NH₂, or alkylamino, including esters, amides, and salts thereof; and W is C(O), C(S), S(O), or SO₂; wherein the compound inhibits a multidrug-resistant retroviral protease. Optionally, R⁵ and R⁶, together the N-W bond of formula (I), comprise a 12- to 18-membered ring. Also provided are pharmaceutical compositions for, and therapeutic methods of, treating a multidrug-resistant retroviral infection in a mammal.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/14120

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D493/04 C07D491/04 C07D495/04 A61K31/34		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 19055 A (NOVARTIS AG) 29 May 1997 (1997-05-29) page 1 -page 14 ---	1, 14
A	WO 96 28463 A (G. D. DEARLE & CO.) 19 September 1996 (1996-09-19) page 4 -page 14, line 12 page 145 -page 189 ---	1, 14
A	WO 95 06030 A (G. D. SEARLE & CO.) 2 March 1995 (1995-03-02) page 4 -page 18, paragraph 21 page 192 -page 212 ---	1, 14
A	WO 94 14793 A (G. D. SEARLE & CO.) 7 July 1994 (1994-07-07) page 3, line 10 -page 13 --- <div style="text-align: right;">-/--</div>	1, 14
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
° Special categories of cited documents :		
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Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">14 December 1999</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">21/12/1999</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Kyriakakou, G</div>

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/14120

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 753 660 A (JAMES A. SIKORSKI ET AL.) 19 May 1998 (1998-05-19) the whole document ----	1,14
A	US 5 728 718 A (RAMNARAYAN S. RANDAD ET AL.) 17 March 1998 (1998-03-17) cited in the application the whole document ----	1,14
A	US 5 723 490 A (ROGER D. TUNG) 3 March 1998 (1998-03-03) the whole document ----	1,14
A	US 5 705 500 A (DANIEL P. GETMAN ET AL.) 6 January 1998 (1998-01-06) the whole document ----	1,14
A	US 5 703 076 A (JOHN J. TALLEY) 30 December 1997 (1997-12-30) cited in the application the whole document ----	1,14
A	US 5 502 060 A (WAYNE J. THOMPSON) 26 March 1996 (1996-03-26) cited in the application the whole document -----	1,14

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 14120

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-21
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 17-21
is are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application. as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 99/14120

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9719055 A	29-05-1997	AU 7623796 A CA 2237016 A EP 0876336 A	11-06-1997 29-05-1997 11-11-1998
WO 9628463 A	19-09-1996	US 5756533 A AU 705268 B AU 5029496 A BR 9607638 A CA 2215061 A CN 1186499 A CZ 9702824 A EP 0813542 A HU 9801562 A NO 974148 A NZ 303861 A PL 322784 A SK 122497 A US 5965601 A US 5968970 A	26-05-1998 20-05-1999 02-10-1996 26-05-1998 19-09-1996 01-07-1998 18-02-1998 29-12-1997 30-11-1998 27-10-1997 25-02-1999 16-02-1998 04-03-1998 12-10-1998 19-10-1999
WO 9506030 A	02-03-1995	US 5843946 A AT 174587 T AU 7669794 A DE 69415326 D DE 69415326 T EP 0715618 A ES 2127938 T GR 3029378 T US 5830897 A US 5786483 A US 5744481 A US 5968942 A	01-12-1998 15-01-1999 21-03-1995 28-01-1999 02-06-1999 12-06-1996 01-05-1999 28-05-1999 03-11-1998 28-07-1998 28-04-1998 19-10-1999
WO 9414793 A	07-07-1994	US 5514801 A AT 148113 T AU 5736494 A CA 2153069 A DE 69307738 D EP 0677048 A JP 8504815 T US 5849784 A	07-05-1996 15-02-1997 19-07-1994 07-07-1994 06-03-1997 18-10-1995 28-05-1996 15-12-1998
US 5753660 A	19-05-1998	AU 7722296 A CA 2236236 A EP 0861249 A WO 9718205 A	05-06-1997 22-05-1997 02-09-1998 22-05-1997
US 5728718 A	17-03-1998	AU 698252 B AU 4378696 A CA 2206787 A EP 0801640 A JP 10504838 T US 5925780 A WO 9619437 A	29-10-1998 10-07-1996 27-06-1996 22-10-1997 12-05-1998 20-07-1999 27-06-1996
US 5723490 A	03-03-1998	US 5783701 A US 5585397 A AU 706732 B	21-07-1998 17-12-1996 24-06-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/14120

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5723490 A		AU 5559696 A	07-11-1996
		BG 102048 A	31-08-1998
		BR 9608032 A	12-01-1999
		CA 2217737 A	24-10-1996
		CN 1181755 A	13-05-1998
		CZ 9703293 A	18-03-1998
		EP 0846110 A	10-06-1998
		HU 9801877 A	28-09-1999
		JP 10509739 T	22-09-1998
		NO 974722 A	13-10-1997
		PL 322877 A	02-03-1998
		SK 143197 A	08-04-1998
		WO 9633184 A	24-10-1996
		US 5977137 A	02-11-1998
		US 5856353 A	05-01-1999
		AP 390 A	02-08-1995
		AT 178598 T	15-04-1999
		AU 691160 B	14-05-1998
		AU 4852093 A	29-03-1994
		BG 99540 A	30-11-1995
		CA 2143208 A	17-03-1994
		CN 1087347 A	01-06-1994
		CZ 9500587 A	13-12-1995
		DE 69324369 D	12-05-1999
		DE 69324369 T	26-08-1999
		EP 0659181 A	28-06-1995
		EP 0885887 A	23-12-1998
		ES 2131589 T	01-08-1999
		FI 951059 A	18-04-1995
		HU 71892 A	28-02-1996
		JP 8501299 T	13-02-1996
		LT 917 A, B	25-11-1994
		NO 950876 A	08-05-1995
		NZ 256238 A	24-04-1997
		NZ 314376 A	28-10-1998
		PL 307858 A	26-06-1995
		SG 43862 A	14-11-1997
		SK 29395 A	13-09-1995
		WO 9405639 A	17-03-1996
US 5705500 A	06-01-1998	AU 711098 B	07-10-1999
		AU 6695196 A	02-10-1996
		BR 9607450 A	30-06-1998
		CA 2215066 A	19-09-1996
		CN 1183767 A	03-06-1998
		CZ 9702822 A	18-02-1998
		EP 0813519 A	29-12-1997
		HU 9800294 A	28-07-1998
		JP 11503414 T	26-03-1999
		NO 974146 A	07-11-1997
		NZ 306026 A	28-01-1999
		PL 322169 A	19-01-1998
		SK 122397 A	04-02-1998
		WO 9628418 A	19-09-1996
		US 5985870 A	16-11-1999
US 5703076 A	30-12-1997	US 5475027 A	12-12-1995
		AT 155779 T	15-08-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. onal Application No

PCT/US 99/14120

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5703076 A		AU 662114 B	24-08-1995
		AU 9085191 A	11-06-1992
		DE 69126987 D	04-09-1997
		DE 69126987 T	05-03-1998
		DK 554400 T	16-02-1998
		EP 0554400 A	11-08-1993
		ES 2059289 T	16-11-1994
		GR 3024586 T	31-12-1997
		JP 6502859 T	31-03-1994
		PT 99551 A	30-10-1992
		WO 9208698 A	29-05-1992
		AT 170169 T	15-09-1998
		AT 164839 T	15-04-1998
		AT 147378 T	15-01-1997
		AT 136888 T	15-05-1996
		AU 9053191 A	11-06-1992
		AU 661667 B	03-08-1995
		AU 9092591 A	11-06-1992
		AU 9125191 A	11-06-1992
		AU 662309 B	31-08-1995
		AU 9133291 A	11-06-1992
		CA 2096407 A	20-05-1992
		CA 2096409 A	20-05-1992
		CA 2096525 A	20-05-1992
		CA 2096528 A	20-05-1992
		DE 69118907 D	23-05-1996
		DE 69124110 D	20-02-1997
		DE 69129235 D	14-05-1998
		DE 69129235 T	12-11-1998
		DE 69130070 D	01-10-1998
		DE 69130070 T	29-04-1999
		DK 558630 T	11-05-1998
		DK 558657 T	07-07-1997
		DK 558673 T	29-07-1996
		EP 0558603 A	08-09-1993
		EP 0558630 A	08-09-1993
		EP 0558657 A	08-09-1993
		EP 0558673 A	08-09-1993
		EP 0735019 A	02-10-1996
		EP 0731088 A	11-09-1996
		EP 0813867 A	29-12-1997
		EP 0815856 A	07-01-1998
		EP 0813868 A	29-12-1997
		ES 2059293 T	16-11-1994
		ES 2059295 T	16-11-1994
		ES 2059294 T	16-11-1994
		ES 2059296 T	16-11-1994
US 5502060 A	26-03-1996	AT 175412 T	15-01-1999
		AU 649170 B	12-05-1994
		AU 2725392 A	29-04-1993
		CA 2081134 A	24-04-1993
		DE 69228106 D	18-02-1999
		DE 69228106 T	15-07-1999
		EP 0539192 A	28-04-1993
		ES 2125251 T	01-03-1999
		JP 1948611 C	10-07-1995
		JP 5239031 A	17-09-1993

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 99/14120

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5502060 A		JP 6078314 B	05-10-1994
		NZ 244773 A	26-10-1994
		WO 9308184 A	29-04-1993
		ZA 9208164 A	03-05-1993
